PETITION
#48C

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on the date appearing below.
ELI LILLY AND COMPANY

By Cheryl J. Boyd Date 10-3-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent No. 4,418,068

Patentee: Charles D. Jones

Assignee: Eli Lilly and Company

Issue Date: November 29, 1983

Attn: Box Patent Ext.

IN RE APPLICANT'S REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Assistant Commissioner for Patents
Washington, D. C. 20231
Sir:

Applicant respectfully requests that the above-captioned application for patent extension under 35 U.S.C. § 156 be amended, supplemented, and reconsidered in the following respects:

Communication

Supplemental Information, Information Disclosure, Disclaimer, and Request

1. As noted in the extension application as filed, applicant initially filed an IND with respect to the approved product on June 18, 1982. Although not expressly stated in the original extension application, this IND nominally became effective on February 16, 1983. Applicant engaged in clinical trials under this IND that ultimately were unsuccessful in that this original IND was inactivated. The inactivation of this IND was noted in the extension application as filed.

2. Applicant's extension application as filed did not set out a chronology of the "regulatory review" activities with respect to the time period during which the inactivated IND was active, *i.e.*, a "brief description of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities." Such a chronology appears to be required under 37 C.F.R. § 1.740(a)(11). Applicant has provided in Supplemental Exhibit A, attached hereto, a revised chronology that sets forth a chronology of significant activities during the pendency of the inactivated IND.

3. Applicant's extension application as originally filed requested a period of extension that was greater than two years, but less than five years. The patent at issue in this extension

application was granted prior to September 24, 1984. To the extent that the effective date of commencement of the "regulatory review period" for the approved product is likewise prior to September 24, 1984, a two-year limit on any otherwise applicable period of extension applies. To the extent that the effective date of the commencement of the "regulatory review period" for the approved product is on or after September 24, 1984, a five-year (rather than two-year) limit on any otherwise applicable period of extension applies.

4. Based on the chronology set out in Supplemental Exhibit A, the nominal commencement of applicant's regulatory review period for the approved product was prior to the date of enactment of 35 U.S.C. § 156, *i.e.*, prior to September 24, 1984. However, for the reasons set out below, applicant asserts that this nominal date is not – and should not be deemed by the U.S. Patent and Trademark Office to be – the effective date of the commencement of the "regulatory review period." The "effective date" being on or after September 24, 1984, applicant respectfully asserts that the five-year limitation should be applied to this extension application.

5. Applicant has filed herewith a disclaimer of rights with respect to that portion of the regulatory review period for the approved product occurring prior to the date of enactment of 35 U.S.C. § 156. Under the terms of this disclaimer, applicant has categorically relinquished the right to take into account, as part of the "regulatory review period," any time period prior to September 24, 1984. Applicant asserts that this disclaimer places applicant in the exact legal and equitable position, for the purposes of this extension application, as an applicant who initially commenced IND activities after the effective date of 35 U.S.C. § 156.

6. Applicant further disclaims any reliance on that portion of the "regulatory review period" between the inactivation of applicant's IND on September 26, 1990 and the effective date of applicant's second IND, June 26, 1992. In determining the regulatory review period, applicant has deducted this time period before determining the applicable regulatory review period.

7. Applicant respectfully requests that the U.S. Patent and Trademark Office and the U.S. Food and Drug Administration calculate the regulatory review period based on the two disclaimers as described above. To assist in making this calculation, Supplemental Exhibit B to this communication sets out applicant's determination of the regulatory review period and the period of extension for which applicant asserts entitlement.

8. In light of the foregoing, applicant respectfully requests that the U.S. Patent and Trademark Office grant to applicant a five-year extension of term. Because the disclaimer-limited regulatory review period (after accounting for the periods disclaimed and the deduction of one-half of the post-disclaimer IND period) is greater than five years, applicant asserts that the five-year limitation provides the operable statutory limitation on the duration of the extension.

Remarks

Information Disclosure; Request for Reconsideration

The nominal date of commencement of the IND period for the approved product was not explicitly set forth in the application for extension as originally filed. This information could be potentially important to the determination of the period of extension to which applicant is entitled. Its omission, although made without any deceptive intent, is nonetheless regretted. As originally filed, the extension application described a pendency of nearly a decade for this IND, including pendency for over two years prior to September 24, 1984. Thus, applicant provided only an implicit indication that this IND was effective during this period.

In order to avoid any possible erroneous determination of the regulatory review period under relevant law, applicant respectfully requests that the extension application be reexamined to take specific account of the above information and to make a determination of the period of extension that is consistent therewith. Specifically, applicant respectfully requests that the application (together with this amendment) be resubmitted to the U.S. Food and Drug Administration (FDA) for the purpose of FDA review of the applicable regulatory review period.

Moreover, in light of the revised regulatory review chronology submitted herewith and the disclaimers set out herein, applicant requests that such reconsideration take account of these disclaimers and the revised chronology.

Request for Extension

Applicant respectfully requests that it be granted a five-year patent term extension. This request is based on a "regulatory review period" effectively commencing on September 24, 1984, the effective date for the Drug Price Competition and Patent Term Restoration Act of 1984 (PTR Act). The complete basis for this request is set forth below.

The length of the "regulatory review period" (adjusted by deducting one-half of the "IND period") for an approved drug product serves as an overall limitation on the length of a patent term extension. Similarly, "effective patent life" (*i.e.*, the time period from the date of regulatory approval to the extended date of patent expiration) similarly serves as a limitation on the duration of a patent extension. Effective patent life cannot exceed 14 years.

In addition to these two limitations, a five-year limitation on the period of extension applies to any extension under 35 U.S.C. § 156. However, for certain *transitional* purposes, only a two-year (rather than five-year) extension is available. This transitional provision is set forth in 35 U.S.C. § 156(g)(6)(C). The two-year, transitional limitation applies only to *certain* patents issued *before September 24,1984*, *i.e.*, patents where the effective date of commencement of the "regulatory review period" was also prior to September 24, 1984.

This two-year, transitional limitation period was enacted by Congress *over sixteen years ago*. This transitional provision was solely intended to prevent pharmaceutical innovators from taking advantage of *pre- September 24, 1984* regulatory review activities. Thus, it was targeted against drugs that were already in advanced stages of development before September 24, 1984.

Otherwise, Congress intended that – in every case – an extension of up to five-years should be available – even for patents issued before September 24, 1984. As an example, if a regulatory review period effectively commenced on September 24, 1984, with an NDA filed in 1994 and NDA approval in 1995, the two-year rule would not apply, *i.e.*, the lengthy regulatory review period would permit up to the full, five-year extension. If, however, the effective IND date commenced a day earlier (*i.e.*, September 23, 1984), the nearly identical regulatory review period could operate on a pre-1984 patent to invoke the two-year limitation – *denying the applicant up to three years of patent restoration.*

The criticality of the September 24, 1984 date is, therefore, paramount. *For making haste to the FDA by one day, a thousand days of extension could be lost.* Such a "thousand for one" penalty – if administered in a categorical manner – would be clearly irrational. Moreover, it would be wholly unsupportable by any conceivable consideration of public policy or manifestation of Congressional intent.

The legislative history of the PTR Act manifests an intent of Congress to provide effective restoration of patent term to spur post-September 24, 1984 drug development efforts – and restore patent term based on these post-1984 activities. The rational limits on the transitional provision can be readily understood from a simple example. It clearly could not have been Congress' intent to create an artificial, irrational, and near absolute incentive to abandon development of a drug that was commenced on September 23, 1984, in favor starting work afresh on a comparable drug product farther up the drug development "pipeline." It would be akin to doubling the winner's purse for the horse who "places" – *after the race has started.* Congress simply cannot have intended that the only means to gain three additional years of patent life from an ongoing drug development campaign would require that an innovator "switch horses" – *and greatly delay the benefits to the public of access to either of the two medicines.*

The only rational and reasoned construction of the transition provisions – one fairly sanctioned by the literal terms of the PTR Act – would bar an innovator from seeking the *simultaneous benefit* of (1) "regulatory delays" before September 24, 1984, and (2) the five-year limitation. An applicant, consistent with the *transitional purpose* of the two-year limitation in the statutory scheme, ought to be entitled to the advantage of one or of the other – just not both.

The U.S. Patent and Trademark Office has long recognized the use of *disclaimers* to obviate an issue of *simultaneous benefit*. For example, the Office has taken the position that an inventor seeking the *simultaneous benefit* of (1) a second patent on a patentably indistinct invention and (2) a separate and independent patent term for both patents cannot do so. However, without violating any aspect of the statutory scheme of Title 35, both the Office and the courts permit a *terminal disclaimer* to be filed. By disclaiming any additional patent term in the second patent, the second and patentably indistinct patent can be validly issued.

Applicant here engaged in early and earnest efforts to accelerate the development of the approved product. This resulted in the filing of an IND before September 24, 1984. If the applicant now seeks the advantage of this pre-1984 period in determining the "regulatory review period," the PTR Act categorically limits any extensions of term at two years. *Applicant has, however, elected to completely disclaim any entitlement to any benefit of any such pre-September 24, 1984 activity.* This disclaimer has placed the applicant in the precise

legal and equitable position of a person who nominally commenced "regulatory review activities" on September 24, 1984. In other words, as a matter of substance, the *effective date* of commencement of "regulatory review activities" for the approved product is now September 24, 1984 – *if the disclaimer is accorded its intended effect.* It necessarily follows, therefore, that applicant should be entitled to the five-year, not two-year, limitation on the duration of the extension.

Applicant believes that this is a case of first impression. Applicant is unaware of any patent extension applicant who has disclaimed any and every benefit from pre-September 24, 1984 regulatory activities in order to produce an effective commencement of the regulatory review period that would be subject to the five-year (rather than two-year) limitation in 35 U.S.C. § 156. Thus, the U.S. Patent and Trademark Office is squarely faced with the novel issue of the manner in which it will implement the transitional provisions of the PTR Act in light of a disclaimer.

As the U.S. Patent and Trademark Office proceeds in resolving this issue of first impression, applicant asserts that recognition of the disclaimer is fully consistent with the statute, the statutory scheme, the statutory intent and legislative history in the PTR Act. As an example of this consistency, nothing would prevent the Office from promulgating a regulation in Title 37 to administratively codify such disclaimer practice – in exactly the same manner that the Office has done so in 37 C.F.R. §§ 1.130(a)(1) and 1.30(b), *i.e.*, terminal disclaimer practice.

As a matter of public policy and intent, Congress acted in 1984 to meaningfully extend patents for post-September 24, 1984 "regulatory delays" at the FDA. It can be assumed, therefore, that Congress would not have mandated the *thousand-fold* penalty noted above – particularly where it would be invoked against a more *diligent* innovator as in preference to a more lackadaisical one. It is clear that Congress could not have intended to create statutory scheme with a categorical incentive to drop development of a promising drug only to start over with a "younger sibling" drug that would take longer to grow into a beneficial new medicine – wholly for the sake of a 1000 days of extra effective patent life.

It is clear, therefore, that the intent of achieving both a *transitional* limitation and an effective restoration is elegantly served by the simple and statutorily consistent mechanism of a disclaimer.

If a "disclaimer" regulation were to be promulgated for this transitional issue, it presumably would merely define the commencement of regulatory review activities under a *substantive test* – the earliest date of reliance on such activities– rather than a *formal test* – the completion of ministerial functions at the FDA that would permit clinical testing to commence. Because such regulatory action is undeniably within the Director's rulemaking discretion, it necessarily represents a proper disposition of the present extension request of first impression.

Moreover, broader principles of statutory construction and administrative implementation clearly afford strong, if not compelling, justification for this disposition. The PTR Act is a classic example of remedial legislation. The complete legislative history makes starkly clear the desire of Congress to compensate inventors for post-1984 regulatory delays by providing effective patent term restoration. In general, the longer the post-1984 regulatory delay the longer the resulting extension – subject to the various policy-driven limitations

discussed above. To achieve, however, the remedial purpose of the PTR Act, a liberal construction of the act is appropriate, if not mandated. Where years and years of post-1984 regulatory delay produce a wasting of the majority of the patent term, Congress undeniably intended effective restoration. The U.S. Patent and Trademark Office has every justification imaginable to use the "effective," rather than "nominal," date for commencement of the regulatory review period to determine the applicability of the transitional provisions of the act – and effect the act's overall remedial purposes.

Finally, appropriateness of giving full force and effect to the disclaimer – and its consonance with the remedial purposes of the PTR Act – is dramatically underscored by the outcome that would be produced in the disposition of this extension application. Applicant's request for a five-year extension is now based wholly on its post- September 24, 1984 activities. The five-year extension would produce an effective patent life ending in 2006 – less than a decade after initial NDA approval of the approved product –more than *five years short of the PTR Act's 14-year limitation on "effective patent life."* As is apparent from the appended chronology, the approved product required *fifteen years* of effort to develop for commercial marketing. Even with a five-year extension, the time to develop this drug would be 50% longer than the drug's effective patent life.

The mathematics for a two-year extension produce *a patent life less than one-half as long as the drug development time*. This limited period of extension would represent a inexplicable application of a "transitional provision" in the PTR Act given the lengthy post-September 24, 1984 "regulatory review period." Applicant's approved product is the active ingredient in Evista® Tablets. This drug has become an important contributor to women's health. It is approved as a safe and effective drug for the prevention and treatment of osteoporosis – a source of profound disability in an aging population. The drug has significant potential to be safe and effective in the prevention of breast cancer and is being extensively evaluated for this use. Except for early, unsuccessful clinical work, this drug was entirely developed through efforts undertaken after September 24, 1984 – presumably beyond any rational reach of any sixteen-year old transitional provision.

Given Evista's development history, there is no principled or rational reason to disregard a disclaimer that merely places the applicant in the exact position it would have been had it initially acted to bring this important product to the market later rather than sooner.

In view of the foregoing, applicant respectfully requests that the accompanying disclaimers be accepted, be given their full and intended effect, and serve as a basis upon which to determine the effective date of commencement of the "regulatory review period." Further applicant requests an administrative determination that the approved product qualifies for the application of the five-year limitation. On this basis, applicant respectfully requests that the Director determine the period of extension to which applicant is entitled under 35 U.S.C. § 156 as five years and so extend the patent.

Respectfully submitted,

Gilbert T. Voy
Attorney for Applicant
Registration No. 43,972
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Eli Lilly and Company
Patent Division/GTV
Lilly Corporate Center
Indianapolis, Indiana 46285

Attachments:
(1) Disclaimer
(2) Supplemental Exhibit A (Due Diligence Chronology For IND 20,486)
(3) Supplemental Exhibit B (Determination of Period of Extension Based on Regulatory Review Activities)

October 2, 2000

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on the date appearing below.
ELI LILLY AND COMPANY

By_____ Date_____

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent No. 4,418,068

Patentee: Charles D. Jones

Assignee: Eli Lilly and Company

Issue Date: November 29, 1983

Attn: Box Patent Ext.

Disclaimer of Applicant

I am authorized to act on behalf of Eli Lilly and Company and specifically authorized to act on behalf of the Company in matters affecting its rights to and under U.S. Letters Patent.

With respect to the above-captioned application for patent term extension, the Company hereby disclaims its rights under Title 35, United States Code, to take any advantage whatsoever of any activities undertaken by or behalf of the Company related in any manner or form to the development and submission of information to the U.S. Food and Drug Administration in connection with regulatory activities related to raloxifene hydrochloride, the active ingredient in Evista® Tablets, taking place before September 24, 1984.

The Company expressly waives, for U.S. patent extension purposes, its right to assert as the effective date for any Investigatory New Drug Application (IND) for raloxifene hydrochloride any date prior to September 24, 1984. The Company hereby expressly disclaims, for U.S. patent extension purposes, any right to claim as a basis for "regulatory review period" any activity prior to September 24, 1984.

By: Robert A Armitage

Robert A. Armitage
Vice President and General Patent Counsel
Registration No. 27,417
Telephone: 317-273-5499

October 2, 2000

SUPPLEMENTAL EXHIBIT A:
DUE DILIGENCE CHRONOLOGY FOR IND 20,486

Date	IND Correspondence Topic
6/18/1982	IND Submission to FDA – Oral Compound LY156758 (antiestrogen) Information supporting Phase I – II Clinical Studies
6/30/1982	Correspondence from William J. Gyartis, M.D. of the FDA acknowledging receipt of the Notice of Claimed Investigational Exemption for a New Drug (IND). IND Number assigned 20,486 Name of drug Oral Compound LY156758 (antiestrogen) Submission date 6/18/82 Receipt 6/21/82
7/26/1982	Note to file regarding a telephone call from Mr. Herbert Behrens, Consumer Safety Office in the Division of Oncology and Radiopharmaceutical Drug Products to F.B. Peck, Jr. M.D. Mr. Behrens was requesting a voluntary 30-day extension because the FDA was unable to complete their review of the preclinical data. The original 30-day wait period expired on 7/22/1982. Dr. Peck agreed to delay starting patients under IND Protocol No. 1 until September 1.
8/12/1982	Correspondence to FDA from F.B. Peck, Jr. M.D. Enclosing an amendment to IND Protocol No. 1 for initial dos ranging and safety of LY156758 in normal male volunteers. Amendment also calls for addition of pharmacokinetic study after the final 200 mg dose. Also confirmed Lilly placed a voluntary hold until 9/1/1982 as requested by Mr. Herbert Behrens, HFD-150 on 7/26/1982
9/14/1982	Correspondence to the FDA from F.B. Peck, Jr. M.D. enclosing additional revision to IND Protocol No.1, submitted 6/18/1982 and amended 8/12/1982. Dr. R.L. Zerbe will be co-investigator with Dr. R.L. Nelson. Included is Dr. Zerbe's Curriculum Vitae and Form FD 1572. Also includes the submission of the label that has been prepared for Clinical Trial Material.

10/14/1982 Correspondence to FDA from F.B. Peck, Jr. M.D. enclosing the IND Protocol Number 2 which outlines a multiple-dose pharmacology study to be conducted by Dr. R.L. Zerbe. Included in the submission is a label that has been prepared for Clinical Trial Material.

10/25/1982 Correspondence to FDA from F.B. Peck, Jr. M.D. that includes a preliminary report of unexpected laboratory value abnormalities encountered in 2 of 4 volunteer subjects enrolled for study under IND Protocol No. 2. Both subjects previously received up to 5 single doses of LY156758 under IND Protocol No. 1. Both subjects exercised strenuously during Protocol No. 2 placebo lead-in period and developed elevated SGOT and LDH values. Subsequent CPK studies indication SGOT and LGH abnormalities were most likely due to muscle damage from vigorous exercise. Also note Lilly has delayed institution of studies under IND Protocol No. 2 until final results are available.

10/29/1982 Correspondence to FDA from F.B. Peck, Jr. M.D. including a report describing the results of further studies. The source of the SGOT and LDH elevations was skeletal muscle and all abnormalities have now returned to normal. Lilly is reinstituting studies under IND Protocol No. 2.

2/16/1983 Correspondence from the William J. Gyarfis, M.D. from the FDA. Mentioned a telephone conversation between Dr. Peck and Dr. Robert S.K. Young, Division of Oncology and Radiopharmaceutical Drug Products. During the conversation, Dr. Peck agreed that the studies will be confined to the sponsor until a clinical brochure has been prepared for guidance of outside investigators and has been submitted to, and found satisfactory by, the FDA.Notice of completion of review and that there is no objection to the initiation of your proposed clinical investigation as originally planned. However, they have added the following recommendations and/or requests that additional information be submitted.

3/15/83	Correspondence to the FDA from H.A. Barnett, M.D. that enclosed the clinical investigator's brochure that will be supplied to outside investigators conducting studies with the compound. Also requested prompt review of the document. Finally, the correspondence enclosed information provided by Dr. Zerbe addressing some of the clinical pharmacology questions in the 2/16 letter from Dr. Gyarfis. Mentioned that Drs. Zerbe and K.E.Briscoe have replaced Dr. R.L. Nelson as clinical monitors. The curriculum vitae for Dr. Briscoe was included.
3/23/1983	Correspondence to the FDA from H.A. Barnett, M.D. that included comments and additional data regarding further toxicological information concerning studies with the compound (in response to the 2/16/1983 letter).
4/14/1983	Correspondence to the FDA from H.A.Barnett, M.D. Enclosed is IND Protocol No. 4 outlining Phase 1 metabolism study using ^{14}C labeled material to be conducted by Dr. Zerbe. Also contained labels that have been prepared for the Clinical Trials Material
5/2/1983	Correspondence to the FDA from H.A. Barnett, M.D. Included IND Protocol No.5 for a study to compare immunologic and endocrine effects of compound with tamoxifen citrate in normal volunteers. Keoxifene hydrochloride has been approved as the generic name for the compound.
6/1/1983	Correspondence from William J. Gyarfis of the FDA stating that they have completed the review of the communication dated 3/15/1983. They have concluded that the restriction on studies by outside investigators is no longer required, and therefore, removed.
6/14/1983	Correspondence to the FDA from H.A. Barnett, M.D. Enclosed the manufacturing – control information supplied in response to the 2/16/1983 letter from Dr. Gyarfis. Also included in the submission are labels prepared for clinical trial material. The World Health Organization has rejected keoxifene hydrochloride for a generic name.
6/30/1983	Correspondence to the FDA from H.A. Barnett, M.D. Enclosed is information, which represents the annual report for the compound. Dr. Zerbe will also conduct a dose-ranging and metabolism study of the hydro-alcoholic solution of LY156758 as outlined in IND Protocol Number 6.
7/12/1983	Correspondence to the FDA from H.A. Barnett, M.D. with a supplement to the annual report submitted 6/30/83. Also contained a report for preclinical pharmacology study conducted in our research labs.
7/26/1983	Correspondence to the FDA from H.A. Barnett, M.D. with IND Protocol number 7 for absorption and metabolism study in normal volunteers using ^{14}C labeled LY156758 in hydro-alcoholic solution.

8/2/1983 Correspondence to the FDA from H.A. Barnett, M.D. with Form FDA 1639 reporting an adverse experience in Patient D.L.W. under Protocol Number 6.

8/3/1983 Correspondence from William Gyarfis, M.D. from the FDA. Reference is made to the Notice of Claimed Investigational Exemption for a New Drug for Compound LY156758. Completed review of submission dated 3/23/1983 and have comments and recommendations.

9/1/1983 Correspondence to the FDA from H.A. Barnett, M.D. Response to FDA letter dated 8/3/1983, the clinical monitor Dr. R.L. Zerbe provided comments.

9/20/1983 Correspondence to the FDA from H.A. Barnett, M.D. Enclosed are the following reports for studies conducted in research laboratories.

- Effects of LY 139481 in Uterine Weight, RNA, DNA, Protein and Water Content in the Uterus of the Immature Rat
- Effects of LY156758 in Accessory Sex Organ Epithelium and Fibromuscular Stroma in the Castrate, Hormone Supplemented Castrate and Intact Sexually Mature Male Guinea Pig

Reports on clinical studies by Zerbe under IND Protocols Numbers 1 & 2. NOTE: LY156758 is the same compound as LY139481-HCl

11/2/1983 Correspondence to the FDA from H.A. Barnett, M.D. IND Protocol Number 8 enclosed, on the study to determine the effects of short-term estrogen administration in normal males. Study will be conducted by Zerbe.

12/7/1983 Correspondence to the FDA from M.W. Talbott, PhD. Studies under IND Protocol Numbers 4 and 7 have been completed. Final reports are included.

2/22/1984 Correspondence to the FDA from M.W. Talbott, PhD. IND Protocol Number 9 outlines a study if compound LY156758 will antagonize the endocrine and chemical changes induced by ethinyl estradiol administration in normal male volunteers. Study by Drs Zerbe and Nelson. The study under IND Protocol Number 6 has been completed and a final report is included on this submission.

5/3/1984 Correspondence to the FDA from M.W. Talbott, PhD. Toxicology laboratory reports are enclosed.

- A Teratology Study of Compound LY156758 Administered Orally to Dutch Belted Rabbits, Toxicology Report Number 12
- Effect of LY156758 on the Induction of Forward Mutation at the Thymidine Kinase Locus of L5178Y Mouse Lymphoma Cells, Toxicology Report Number 13.

6/20/1984 Correspondence to the FDA from M.W. Talbott, PhD. Annual Report. Also Dr. Zerbe also informed that the study under IND Protocol Number 5 never was initiated because of potential problems with bioavailability of LY156758. Major objectives of this study are addressed in IND Protocol Number 9.

7/20/1984 Correspondence to the FDA from Robert A. Browne, M.D. Report on study in immature overiectomized rats.

8/21/1984 Correspondence to the FDA from Robert A. Browne, M.D. Report entitled "A One-Year Chronic Toxicity Study of Compound LY156758 Administered Orally to Fischer 344 Rats"

10/25/1984 Note to File from R.A.Browne, M.D. Dr. Talbott received a call from Dr. Stolzenberg at the FDA regarding some concerns on toxicology studies done on LY156758. Dr. Browne called back on 10/23/84 to clarify. Subsequent review of the submission reveals that a summary of the ophthalmologic examination in the 6 month dog study were submitted to the agency in Volume 4 of Lilly's submission. This information will be forwarded to Dr. Stolzenberg. This still leaves the issue of performing and the reporting of ophthalmologic examinations on the other chronic toxicity studies. These will be addressed with Dr. Emmerson.

10/29/1984 Note to file from R.A.Browne. Dr. Browne called Dr. Stolzenberg on 10/26 in follow-up to his inquiry. Told him of location of the 6-month dog study. Dr. Stolzenberg stated that he reviewed the 6-month rat and 12-month rat studies (12 month submitted August 1984) and could find no similar data there. Dr. Browne said it would be discussed with the toxicology section and given to the FDA as soon as feasible.

10/29/1984 Note to File (memo addressed to Dr. J.L. Emmerson from Dr. Browne) Reiterating that the FDA wants results reported on ophthalmologic examinations on all chronic and sub-chronic studies with this class of

drugs. Asking Emmerson to forward information to him (Browne) so that it may be forwarded to the FDA and Dr. Stolzenberg specifically.

10/30/1984 Note to File (memo addressed to Dr. N.V. Owen from Dr. Browne). Requesting the agency's desire to have detailed reports on ophthalmologic toxicity for this compound (wanted this reported for the entire group of antiestrogen compounds). Suggest a brief summary, at the least, of the eye findings in each of these two studies, 6-month and 12-month rat, be prepared and sent to Browne to transmit to the FDA as soon as possible.

10/30/1984 Correspondence to the Dr. Stolzenberg of the FDA from Dr. Browne. Letter in response to the discussion regarding IND 20486. Gives specifics of ophthalmologic examinations of 6-month dog study. 6-month chronic toxicity on rated submitted in Volume 2 and stating a brief summary of eye exam in two studies will be forwarded to Dr. Stolzenberg

11/7/1984 Correspondence to the FDA from Dr. Robert Browne. Follow-up letter to letter dated 10/30/1984

12/3/1984	Note to File from Dr. Browne. Telephone conversation with Dr. Richard Podliska at the FDA regarding LY156758. Dr. Podliska called 11/30 and reached Dr. Talbott's secretary. Dr. Browne reached Dr. Podliska on 12/3/1984. Instructions from Dr. Podliska in view of "carcinogenicity in animals in studies of tamoxifen" the drug should not be given to normal male volunteers as outlined in Protocol Number 9. The study was completed on 6/20/1984. Final report of the study should be available within the next week. Dr. Zerbe was consulted and relayed message to Dr. Podliska. Dr. Podliska was not aware of any new data on tamoxifen regarding carcinogenicity. Dr. Browne explained interest of a brief summary of any new data on antiestrogens as it might affect the design of further studies. Dr. Podliska stated they should ask formally for an explanation of the FDA request to terminate the plans for the study in the cover letter of that submission. Will discuss further with Dr. J.H. Marsden and Dr. Zerbe.
1/4/1985	Correspondence from the John F. Palmer, M.D, of the FDA to Dr. Talbott. Reference is made to the Notice of Claimed Investigational Exemption for a New Drug LY156758 and telephone conversation of 11/30/1984 between Ms. Sharon Arnold and Dr. R.J. Podliska relative to the amendment dated 2/22/1984. During the telephone conversation, it was requested and agreed that the drug should not be given to normal male volunteers as proposed in Protocol Number 9 and report of use of the drug should be submitted in the event that the study had already progress to that juncture.
1/8/1985	Correspondence to the FDA from Dr. Browne stating that Dr. Zerbe has completed the study under IND Protocol Number 8 to determine the effects of short-term estrogen administration on normal subjects. Final report is enclosed.
1/28/1985	Correspondence to the FDA from Dr. Browne stating in the final report sent on 1/8/1985 that there were some figures not reproduced in color. Without color, the figures cannot be interpreted. The correct pages were sent to substitute with those referred to in the letter.
1/31/1985	Correspondence to the FDA from Dr. Browne stating Dr. Aman U. Buzdar will conduct a study of LY156758 in the treatment of patients with metastatic breast cancer as outlined in IND Protocol Number 3. Dr. Buzdar's Curriculum Vitae and Form FD 1573 was enclosed.
3/5/85	Toxicology studies
6/17/85	Annual Report submitted to FDA
6/18/86	Annual Report submitted to FDA
2/7/1987	Correspondence to the FDA from Dr. Robert A. Browne. Final report on the study under IND Protocol Number 9 by Drs. Nelson and Zerbe.

6/19/87	Annual Report submitted to FDA
6/13/88	Annual Report submitted to FDA
6/12/89	Annual Report submitted to FDA
6/18/90	Annual Report submitted to FDA
9/26/90	Request to inactivate the IND submitted to FDA
10/25/90	Letter responding to call from Ms. Ellen Cutler of DMEDP. We responded that no studies are being carried out, none are anticipated and all of the unused drug had been destroyed or accounted for by the company.
11/19/90	FDA letter inactivating IND.

SUPPLEMENTAL EXHIBIT B:
Determination of Period of Extension Based on Regulatory Review Activities

Patent Extension Calculation	Calculations
Date IND Becomes Effective	February 16, 1983
Date NDA Submitted to the FDA	June 9, 1997
Date NDA Approved by the FDA	December 9, 1997
Patent Issue Date	November 29, 1983
U.S. Non-provisional Effective Patent Filing Date	April 3, 1981
U.S. Non-provisional Actual Patent Filing Date	December 16, 1981
Patent Terminal Disclaimer Date (As Applicable)	NA
17 Years from Issue Date	November 29, 2000
20 Years from Filing Date	April 3, 2001
Greater of 17 Years from Issue or 20 Years from Filing	April 3, 2001
Greater of 17/20 Year Terms, If Applicable and Longer	April 3, 2001
Actual Patent Term (Including Applicable Disclaimer)	April 3, 2001
Post-Patent Issuance Start of Regulatory Review	November 29, 1983
Date of Disclaimer for 2-Year Transitional Provision	September 24, 1984
Revised Start Date (Including Applicable Disclaimer)	September 24, 1984
Total Post-9/9/84 IND Review Period (days)	4,642
Start Date of IND Deduction	September 26, 1990
End Date of IND Deduction	June 26, 1992
Further IND Deduction (days)	639
Net IND Period	4,003
1/2 IND Review Period (days)	2,002
NDA Review Period (days)	184
Regulatory Review Period (days)	4,187
NDA Period + 1/2 IND Period (days)	2,186
Expiration Date of 5 Year Limitation Period	April 3, 2006
Five Year Limitation Period in Days	1,826
Maximum Extension Period Before 14 Year Limit	1,826
Expiration Date Before Applying 14 Year Limit	April 3, 2006
Expiration of 14 Years from NDA Approval	December 9, 2011
Expiration Date Applying 14 Year Limit	April 3, 2006
Statutory Extension Period in Days	**1,826**